REMARKS

Claims 14, 21, 22 and 28-34 are pending in the instant application. Claims 14, 21, 22 and 28-34 have been rejected. Claims 14 and 28-34 have been canceled. Claim 21 has been amended. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Rejection of Claims Under 35 U.S.C. 102(b)

The rejection of claims 14, 21, 22 and 28-33 as being anticipated by Karin et al. (US Patent 5,837,244) has been maintained for reasons of record. The Examiner suggests that this reference discloses protein kinases JNK1 and JNK2 and the use of a reagent that modulated JNK activity as a way to treat a cell proliferative disorder, including the general teaching of antisense of about 15 mer. Applicants respectfully disagree with the Examiner's conclusions regarding this reference.

A careful review of the patent of Karin et al. (US Patent 5,837,244) fails to provide any JNK sequence information whatsoever. This reference supports the isolation of JNK protein and biochemical characterization of the JNK protein's ability to bind and phosphorylate the c-Jun protein. However, this patent

fails to teach or suggest the polypeptide sequence of the JNK protein much less any polynucleotide sequence encoding a JNK protein. Instead, Karin et al. suggest various ways in which a polynucleotide sequence encoding JNK might be obtained using hybridization or antibody screens of cDNA libraries, or PCR. This patent also suggests that a polynucleotide sequence encoding JNK can be deduced from the genetic code provided the degeneracy of the genetic code is taken into account. However, such deduction is not possible without disclosure of the polypeptide sequence, and this sequence is not provided by the Karin et al. reference.

Karin et al. teach that antisense nucleic acids are DNA or RNA molecules that are complementary to at least a portion of a specific mRNA molecule (see column 8, lines 49-51), making it clear that antisense molecules cannot be designed without specific sequence information for the specific mRNA molecule targeted. It has long been the rule that because the degeneracy of the genetic code gives rise to large numbers of different potential sequences capable of encoding a given polypeptide sequence, disclosure of a polypeptide sequence does not necessarily render obvious a specific nucleic acid sequence encoding that sequence. "[A] prior art disclosure of the amino acid sequence of a protein does not

necessarily render particular DNA molecules encoding the protein obvious because the redundancy of the genetic code permits one to hypothesize an enormous number of DNA sequences coding for the protein. No particular one of these DNAs can be obvious unless there is something in the prior art to lead to the particular DNA and indicate that it should be prepared." In re Deuel, 51 F.3d, 1552, 1558-1559, 34 USPQ2d, 1210, 1215 (Fed. Cir. 1995). According to this reasoning, because the disclosure of a JNK polypeptide sequence would fail to render obvious claims to a specific mRNA or a cDNA molecule encoding the protein, it should also not render obvious even generic claims to an antisense molecule complementary to those same specific mRNA or cDNA molecules encoding a protein. Thus, given the absence of even a JNK polypeptide sequence in Karin's disclosure, Karin et al. fails to provide more than the most generalized type of incentive to make antisense against JNK, and cannot anticipate the instant claims. Withdrawal of this rejection is therefore respectfully requested.

II. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claims 14, 21, 22 and 28-34 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not

described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner suggests that the specification broadly claims oligonucleotides that hybridize with JNK2 gene but that the applicant has not made clear the genus of the claimed compounds. Claims 14, 21, 22 and 28-34 have also been rejected under 35 U.S.C. 112, first paragraph, because the specification, does not enable any person skilled in the art to which it pertains, or is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The Examiner acknowledges that the specification is enabling for a method of inhibiting growth of a breast tumor in an animal comprising administration of SEQ ID NO: 31 but suggests that the specification does not provide enablement for a method of inhibiting any tumor growth in any animal using any oligonucleotide targeted to JNK2. Applicants respectfully traverse these rejections under 35 U.S.C. 112, first paragraph.

At the outset, in an earnest effort to advance the prosecution of this case, Applicants have canceled claims 14 and 28-34 and amended the remaining claims to refer to methods of inhibiting breast tumor cell growth in an animal using a specific antisense

compound, an oligonucleotide that is targeted to human JNK2 as disclosed in Table 8 of the specification as filed.

However, Applicants disagree with the Examiner's suggestion that the cited references support the position that application of antisense *in vivo* is highly unpredictable or problematic.

The Examiner has pointed to articles concerning the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable and that predicting efficacy based on *in vitro* data is problematic. However, when one reads each of the papers as a whole, as required under MPEP 2141.02, these references actually teach the potential usefulness of this class of drugs in humans, and more importantly fail to provide any reasonable basis to doubt the pharmacological activity observed in cells in the instant invention would also occur in humans. Therefore, what these papers cited by the Examiner actually teach is that antisense oligonucleotides must be developed using well designed studies that progress logically from activity in cells to activity in animals, and then to testing in humans. Nowhere in the references cited do the authors state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity in humans.

Branch (1998) is cited by the Examiner in support of her position. This paper teaches the need to develop antisense molecules based on sound data and careful screening, such as is presented in the instant specification. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects in humans is unpredictable. The Examiner, however, attempts to use this paper to support suggestions concerning the inaccessibility of most potential target RNA binding sites to antisense molecules and the unpredictability of antisense effects. One of skill in the art would not expect to predict the winning antisense compound *a priori*, but would screen a reasonable number of compounds in order to find the one best suited to his or her needs. Time and difficulty of experiments are not determinative of enablement if they are merely routine. Quantity of examples is only one factor that must be considered before reaching the final conclusion that undue experimentation would be required. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.(MPEP 2164.06). The fact that effective antisense drugs are selected from large pools of candidates and then optimized, rather than predicted *a priori*, does not indicate lack of enablement, *i.e.*, the need for undue experimentation. "The test is not merely quantitative, since a considerable amount of

experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

Furthermore, the need to select an antisense compound from a pool of candidates is not unique to antisense drugs; all drugs are selected from large pools of candidates. Only five in 5,000 compounds make it from early research and preclinical testing to clinical trials, and of those five that enter clinical trials only one is approved (data from PhRMA, Pharmaceutical Research and Manufacturers of America).

The Office Action cites Branch as supporting the unpredictability of non-antisense effects. The predictability, or lack thereof, of an effect which is not the claimed invention is irrelevant. One of ordinary skill is well aware of how to use proper controls to elucidate antisense inhibition of a desired target. Branch is also cited as teaching the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its

dose-response curves and therapeutic index is available. However, as discussed *supra*, the teachings of a reference must be read in its entirety, not only in bits and pieces to support the Examiner's interpretation. See MPEP 2141.02. The full excerpt which has been cited in part by the Examiner begins, "As is true of all pharmaceuticals, the value of a potential antisense drug"... In other words, antisense drugs are no different from any other drugs. If the need for evaluation of dose-response and therapeutic index were a bar to patentability, no drug would be patentable. Clearly this is not the proper standard. Thus nowhere does the reference of Branch teach that one of skill would be unable to use the compounds or methods of the invention in an *in vivo* environment.

Two of the other references cited by the Examiner, Jen et al. (2000) and Dias (2002), likewise provide no basis to conclude that extrapolation from *in vitro* data to effects in humans is unpredictable or especially problematic.

With respect to the Examiner's comments regarding the lack of guidance for delivery of antisense compounds, Applicants assert that if a compound is shown to be active after intravenous administration, a route where the drug in question can distribute

widely in the body and not only to the needed site of action, these data would be more than adequate evidence to one of skill that a more local and direct route of administration, such as intravitreal, intraventricular, intraluminal, intravesicial, or intrathecal, would result in delivery of the active compound in sufficient amount to produce a pharmacological effect.

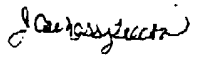
In addition, the Examiner has failed to support the proposition that administration of antisense to JNK2 would be unpredictable based on any objective evidence. In contrast, data are provided in the specification as filed showing the selection and design of antisense oligonucleotides to selected targets and their activity *in vitro* as well as *in vivo*. Therefore, Applicants have clearly met their burden under 112, first paragraph. Further, Applicants respectfully remind the Examiner that the "absence of working examples should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement and the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation". In re Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)). (MPEP 2164.02).

Accordingly, based on these arguments and the amendments to the claims, withdrawal of this rejection is respectfully requested.

III. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,



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